Regeneration (biology)

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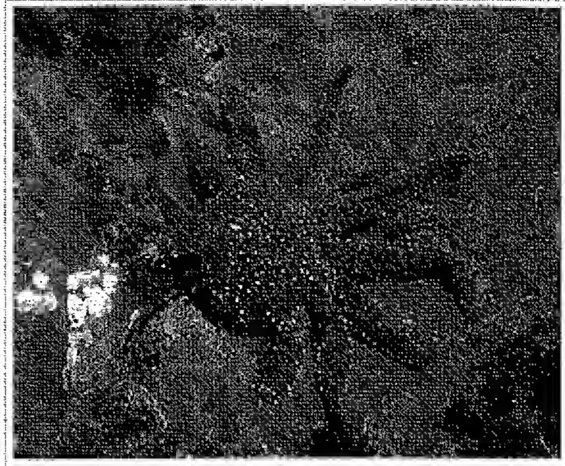
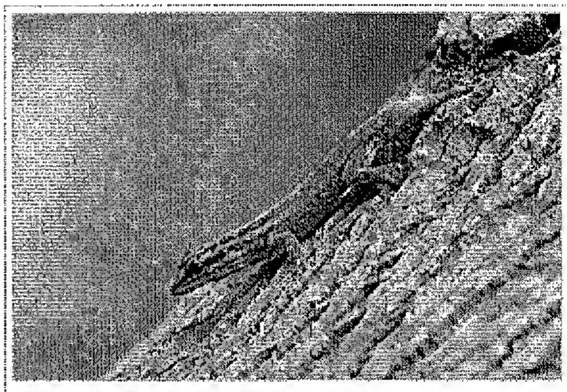


Sun flower sea star regenerates its arms



Dwarf yellow-headed gecko with regenerating tail

In biology, **regeneration** is the process of renewal, restoration, and growth that makes genomes, cells, organs, organisms, and ecosystems resilient to natural fluctuations or events that cause disturbance or damage. Every species is capable of regeneration, from bacteria to humans.[1][2] At its most elementary level, regeneration is mediated by the molecular processes of DNA synthesis.[3][4] Regeneration in biology, however, mainly refers to the morphogenic processes that characterizes the phenotypic plasticity of traits allowing multi-cellular organisms to repair and maintain the integrity of their physiological and morphological states. Above the genetic level, regeneration is fundamentally regulated by asexual cellular processes.[5]

The hydra and the planarian flatworm have long served as model organisms for their highly adaptive regenerative capabilities.[6] Once wounded, their cells become activated and start to remodel tissues and organs back to the pre-existing state.[7] The urodele (salamander), an amphibian, is possibly the most adept vertebrate order for their capability of regenerating limbs, tails, jaws, eyes and a variety of internal structures.[1] The regeneration of organs is a common and widespread adaptive capability among metazoan creatures.[6] In a related context, some animals are able to reproduce asexually through fragmentation, budding, or fission.[5] A planarian parent, for example, will constrict, split in the middle, and each half generates a new end to form two clones of the original.[8] Echinoderms, such as the starfish, crayfish, many reptiles, and amphibians exhibit remarkable examples of tissue regeneration. The case of autotomy, for example, serves as a defensive function as the animal detaches a limb or tail to avoid capture. After the limb or tail has been autotomized, cells move into action and tissues regenerate.[9][10][11] Ecosystems are regenerative as well. Following a disturbance, such as a fire or pest outbreak in a forest, pioneering species will occupy, compete for space, and establish themselves in the newly opened habitat. The new growth of seedlings and community assembly process is known as regeneration in ecology.[12][13]

Contents

Cellular molecular fundamentals

Pattern formation in the morphogenesis of an animal is regulated by genetic induction factors that put cells to work after damage has occurred. Neural cells, for example, express growth-associated proteins, such as GAP-43, tubulin, actin, an array of novel neuroptides, and cytokines that induce a cellular physiological response to regenerate from the damage.[14] Many of the genes that are involved in the original development of tissues are reinitialized during the regenerative process. Cells in the primordia of zebrafish fins, for example, express four genes from the homeobox *msx* family during development and regeneration.[15]

Tissues and organs

"Regenerative strategies include the rearrangement of pre-existing tissue, the use of adult somatic stem cells and the dedifferentiation and/or transdifferentiation of cells, and more than one mode can operate in different tissues of the same animal. All these strategies result in the re-establishment of appropriate tissue polarity, structure and form."[16]:873 During the developmental process genes are activated that serve modify the properties of cell as they differentiate into different tissues. Development and regeneration involves the coordination and organization of populations cells into a blastema, which is "a mound of stem cells from which regeneration begins."[17] The dedifferentiation of cells means that they lose their tissue specific characteristics as tissues remodel during the regeneration process. The transdifferentiation of cells means that they lose their tissue specific characteristics during the regeneration process and then re-differentiate to a different kind of cell.[16]

Model organisms in Bilateria

Planaria (Platyhelminthes)

Planaria exhibit an extraordinary ability to regenerate lost body parts. For example, a planarian split lengthwise or crosswise will regenerate into two separate individuals. In one experiment, T. H. Morgan found that a piece corresponding to 1/279th of a planarian could successfully regenerate into a new worm. This size (about 10,000 cells) is typically accepted as the smallest fragment that can regrow into a new planarian. Regeneration of planaria is epimorphic regeneration. After amputation, stump cells form blastema.

Vertebrates

Amphibians

Limb regeneration in newts occurs in two major steps, first de-differentiation of adult cells into a stem cell state similar to embryonic cells and second, development of these cells into new tissue more or less the same way it developed the first time.[18] Simpler animals like planarian have an enhanced capacity to regenerate because the adults retain clusters of stem cells (neoblast) within their bodies which migrate to the parts that need healing. They then divide and differentiate to grow the missing tissue and organs back.

In salamanders, the regeneration process begins immediately after amputation. Limb regeneration in the axolotl and newt have been extensively studied. After amputation, the epidermis migrates to cover the stump in less than 12 hours, forming a structure called the apical epidermal cap (AEC). Over the next several days there are changes in the underlying stump tissues that result in the formation of a blastema (a mass of dedifferentiated proliferating cells). As the blastema forms, pattern formation genes – such as HoxA and HoxD – are activated as they were when the limb was formed in the embryo.[19][20] The distal tip of the limb (the autopod, which is the hand or foot) is formed first in the blastema. The intermediate portions of the pattern are filled in during growth of the blastema by the process of intercalation.[18][19] Motor neurons, muscle, and blood vessels grow with the regenerated limb, and reestablish the connections that were present prior to amputation. The time that this entire process takes varies according to the age of the animal, ranging from about a month to around three months in the adult and then the limb becomes fully functional.

In spite of the historically few researchers studying limb regeneration, remarkable progress has been made recently in establishing the neotenous amphibian the axolotl (*Ambystoma mexicanum*) as a model genetic organism. This progress has been facilitated by advances in genomics, bioinformatics, and somatic cell transgenesis in other fields, that have created the opportunity to investigate the mechanisms of important biological properties, such as limb regeneration, in the axolotl.[21] The Ambystoma Genetic Stock Center (AGSC) is a self-sustaining, breeding colony of the axolotl supported by the National Science Foundation as a Living Stock Collection. Located at the University of Kentucky, the AGSC is dedicated to supplying genetically well-characterized axolotl embryos, larvae, and adults to laboratories throughout the United States and abroad. An NIH-funded NCRR grant has led to the establishment of the Ambystoma EST database, the Salamander Genome Project (SGP) that has led to the creation of the first amphibian gene map and several annotated molecular data bases, and the creation of the research community web portal.[22]

Mice

The mechanism for regeneration in MRL mice has been found and it is related to the deactivation of the p21 gene.[23][24]

Adult mammals have limited regenerative capacity compared to most vertebrate embryos/larvae, adult salamanders and fish. The MRL mouse is a strain of mouse that exhibits remarkable regenerative abilities for a mammal. Study of the regenerative process in these animals is aimed at discovering how to duplicate them in humans.

By comparing the differential gene expression of scarless healing MRL mice and poor healing C57BL/6 mice strain, 36 genes have been identified that are good candidates for studying how the healing process differs in MRL mice and other mice.[25][26]

The regenerative abilities of MRL mice does not, however, protect them against myocardial infarction, as heart regeneration in adult mammals (neocardiogenesis) is limited because heart muscle cells are nearly all terminally differentiated. MRL mice show the same amount of cardiac injury and scar formation as normal mice after a heart attack.[27] Though recent studies provide evidence that this may not be the case, and that MRL mice do regenerate from heart damage. [2] (http://www.eurekalert.org/pub_releases/2001-08/wi-rit080201.php)

Humans

Fingertips

Studies in the 1970s showed that children up to the age of 10 or so who lose fingertips in accidents can regrow the tip of the digit within a month provided their wounds are not sealed up with flaps of skin – the de facto treatment in such emergencies. They normally won't have a finger print, and if there is any piece of the finger nail left it will grow back as well, usually in a square shape rather than round.[28][29]

In August 2005, Lee Spievack, then in his early sixties, accidentally sliced off the tip of his right middle finger just above the first phalanx. His brother, Dr. Alan Spievack, was researching regeneration and provided him with powdered extracellular matrix, developed by Dr. Stephen Badylak of the McGowan Institute (http://www.mirm.pitt.edu/) of Regenerative Medicine. Mr. Spievack covered the wound with the powder, and the tip of his finger re-grew in four weeks.[30] The news was released in 2007. Lee Spievack is the first documented case of an adult human regenerating fingertips;[28] however, Ben Goldacre has described this as "the missing finger that never was", claiming that fingertips regrow and quoted Simon Kay, professor of hand surgery at the University of Leeds, who from the picture provided by Goldacre described the case as seemingly "an ordinary fingertip injury with quite unremarkable healing"[31]

A similar story was reported by CNN. A woman named Deepa Kulkarni lost the tip of her little finger and was initially told by doctors that nothing could be done. Her personal research and consultation with several specialists including Badylak eventually resulted in her undergoing regenerative therapy and regaining her fingertip.[32]

Ribs

There have appeared claims that human ribs could regenerate if the periosteum, the membrane surrounding the rib, were left intact. In one study rib material was used for skull reconstruction and all 12 patients had complete regeneration of the resected rib.[33]

Liver

The human liver is one of the few glands in the body that has the ability to regenerate from as little as 25% of its tissue.[34] This is largely due to the unipotency of hepatocytes.[35] Resection of liver can induce the proliferation of the remained hepatocytes until the lost mass is restored, where the intensity of the liver's response is directly proportional to the mass resected. For almost 80 years surgical resection of the liver in rodents has been a very useful model to the study of cell proliferation.[36][37]

Kidney

Regenerative capacity of the kidney remains largely unexplored. The basic functional and structural unit of the kidney is nephron, which is mainly composed of four components: the glomerulus, tubules, the collecting duct and peritubular capillaries. The regenerative capacity of the mammalian kidney is limited compared to that of lower vertebrates.

In the mammalian kidney, the regeneration of the tubular component following an acute injury is well known. Recently regeneration of the glomerulus has also been documented. Following an acute injury, the proximal tubule is damaged more, and the injured epithelial cells slough off the basement membrane of the nephron. The surviving epithelial cells, however, undergo migration, dedifferentiation, proliferation, and redifferentiation to replenish the epithelial lining of the proximal tubule after injury. Recently, the presence and participation of kidney stem cells in the tubular regeneration has been shown. However, the concept of kidney stem cells is currently emerging. In addition to the surviving tubular epithelial cells and kidney stem cells, the bone marrow stem cells have also been shown to participate in regeneration of the proximal tubule, however, the mechanisms remain controversial. Recently, studies examining the capacity of bone marrow stem cells to differentiate into renal cells are emerging.[38]

Like other organs, the kidney is also known to regenerate completely in lower vertebrates such as fish. Some of the known fish that show remarkable capacity of kidney regeneration are goldfish, skates, rays, and sharks. In these fish, the entire nephron regenerates following injury or partial removal of the kidney.

Heart

Several animals can regenerate heart damage, but in mammals cardiomyocytes cannot proliferate and heart damage causes scarring and fibrosis.

The long held view was that mammalian cardiomyocytes are terminally differentiated and cannot divide. However inhibition of p38 MAP kinase was found to induce mitosis in adult mammalian cardiomyocytes.[39] Treatment with FGF1 and p38 MAP kinase inhibitors regenerates the heart, reduces scarring, and improves cardiac function in rats with cardiac injury.[40]

Notes

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External links

- Spallanzani's mouse: a model of restoration and regeneration (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14594211)
- Mice that regrow hearts in the news (http://www.worldhealth.net/news/it_s_a_miracle_-_mice_regrow_hearts/)

- DARPA Grant Supports Research Toward Realizing Tissue Regeneration (http://www.upmc.com/Communications/NewsBureau/Research/Articles/DarpaGrant.htm)
- The Geniuses Of Regeneration (http://businessweek.com/magazine/content/04_21/b3884008_mz001.htm) in *BusinessWeek*, May 24, 2004
- UCI Limb Regeneration Lab (http://regeneration.bio.uci.edu)

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